Are maternal smoking and stress during pregnancy related to ADHD symptoms in children?

Alina Rodriguez and Gunilla Bohlin
Department of Psychology, Uppsala University, Sweden

Background: There are some indications that maternal lifestyle during pregnancy (smoking and stress) contributes to symptoms of ADHD in children. We prospectively studied whether prenatal exposure to maternal smoking and/or stress is associated with ADHD symptoms and diagnostic criteria (according to DSM-IV) in 7-year-olds. Methods: Nulliparous Scandinavian women were consecutively recruited at their first prenatal health care visit and assessments of smoking and stress were collected at gestational weeks 10, 12, 20, 28, 32, and 36. Children were followed up at 7 years old. We obtained full data for 72% of the sample: ADHD symptoms were rated by 74% of mothers (n = 290) and 96% of eligible teachers (n = 208). Attrition analyses showed no differences on key variables between participants and non-participants at follow-up. Results: Results of multiple regression analyses showed prenatal exposure to smoking (β = .16, p < .01) and stress (β = .18, p < .01) were independently associated with later symptoms of ADHD. Results of logistic regression analyses showed that fulfillment of the diagnostic criteria for ADHD was related to exposure to prenatal stress (β = .68, p < .01) especially in boys. The results were not confounded by sociodemographic factors or birth outcomes. Conclusions: This study provides evidence that prenatal exposure to stress and smoking is independently associated with later symptoms of ADHD in human children, particularly for boys. Because stress and smoking are relatively common during pregnancy, and yet preventable, these results are of public health significance. Keywords: Prenatal exposure, maternal lifestyle during pregnancy, ADHD, inattention, hyperactivity–impulsivity, timing.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention and/or hyperactivity that persist for at least 6 months, across multiple settings, and which interfere with developmentally appropriate functioning (American Psychiatric Association, 1994). ADHD is the most commonly diagnosed childhood psychiatric disorder, with an estimated prevalence rate of at least 4% (Brown et al., 2001). Even though symptoms of a large percentage of children with ADHD may become less adverse with age, impairments are often still apparent in adulthood (Bresnahan & Barry, 2002; Mannuza & Klein, 2000; McKay & Haperin, 2001; Wilens, Biederman, & Spencer, 2002). The causes of ADHD are still not understood, but both genetic (Smalley et al., 2002) and environmental factors have been implicated (Rietveld, Hudziak, Bartels, Van Beijsterveldt, & Boomsma, 2003). There is some evidence suggesting that prenatal environmental contributions to the etiology of ADHD (Linnet et al., 2003). The purpose of this study was to investigate to what extent maternal smoking and psychosocial stress during pregnancy impact upon symptoms typically associated with ADHD in children.

A number of retrospective studies have investigated whether maternal smoking is related to inattention or hyperactivity in children and have found significant effects (e.g., Fried, 1995; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002; Orlebeke, Knol, & Verhulst, 1999; Weissman, 1999), while others have not (e.g., McGee & Stanton, 1994; Wakschlag et al., 1997; Weitzman, Gortmaker, & Sobol, 1992). Besides the obvious methodological inadequacy of assessing prenatal smoking retrospectively, other limitations include assessing smoking as a dichotomized variable, not reporting results by gender, only studying one type of symptom (e.g., hyperactivity or inattention), and not studying representative samples. Some, but not all, of these limitations have been addressed in several prospective studies which have shown inconsistent results (e.g., Fried and Watkinson, 2001; Kotimaa et al., 2003; Wasserman, Liu, Pine, and Graziano, 2001; Cornelius, Ryan, Day, Goldschmidt, & Willford, 2001). Because these studies use different instruments, measuring global behavior problems rather than ADHD per se (some lacking validation), a clear picture does not emerge concerning the link between prenatal smoke exposure and symptoms specifically related to ADHD. Further methodological problems present in the prospective studies include use of nonrepresentative samples (e.g., Leech, Richardson, Goldschmidt, & Day, 1999) and selective attrition (e.g., Bor et al., 1997).

A number of biologically plausible mechanisms derived from correlational findings in human studies have been experimentally tested in animal models. Animal studies based on multiple methods and using multiple species demonstrate that prenatal exposure to nicotine leads to hyperactivity in the...
offspring (e.g., Muneoka et al., 1997; Weinstock, 2001). Recently Roy and colleagues (Roy, Seidler, and Slotkin, 2002) found that prenatal nicotine exposure elicited structural changes and compromised neuronal maturation. More importantly, these initial changes profoundly influenced the development of cells that emerged later on during postnatal life. Nicotine has been found to cause dysfunction of the dopaminergic system, which is consistent with observations that children with ADHD also have a similar dysfunction (Ernst et al., 1999). In sum, the evidence to date points to plausible biological mechanisms that could account for the ADHD–prenatal nicotine exposure link.

Again, because of inherent difficulties in human research, animal models have been extensively used to test whether prenatal stress causes neurobehavioral disturbance in the offspring. Work on rodents shows that depending on the time of exposure, specific neurobehavioral perturbation results in the offspring (Chapillon, Patin, Roy, Vincent, & Caston, 2002), such as altered activity levels (Diaz, Ogren, Blum, & Fuxe, 1995; Lordi, Patin, Protais, Mellier, & Caston, 2000), increased emotionality (Lordi, Protais, Mellier, & Caston, 1997) and altered dopaminergic and serotonergic functioning (Muneoka et al., 1997). Disturbances are evident even into adulthood (Suchecki & Neto, 1991). The work by Schneider and coworkers on primates of various species has demonstrated attentional (Schneider & Coe, 1993), behavioral (Clarke & Schneider, 1997), and motoric disturbances (Schneider, 1992) as well as alterations in structural brain anatomy (Coe, Lulbach, & Schneider, 2002) and dopaminergic functioning (Schneider et al., 1998) in offspring as a result of experimentally induced social or emotional stress in the pregnant female. As with rodents, neurobehavioral effects have also been found to be long lasting in primates (Schneider et al., 1998), which suggests that prenatal events, such as stress, permanently change the animal’s developmental trajectory.

Only a few studies of prenatal stress and child behaviors in humans have been conducted. As with the studies on smoking during pregnancy, investigations on the association between prenatal stress and ADHD symptoms in humans are fraught with a variety of shortcomings. Some retrospective studies have found prevalence of child behavior problems related to ADHD as a function of prenatal stress (McIntosh, Mulkins, & Dean, 1995; Stott, 1973; Ward, 1991) while others have not (Meijer, 1985). Prospective data show that prenatal stress is associated with disturbed attention regulation (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002) and activity (Van den Bergh, 1992) in infants. Recent investigations (O'Connor, Heron, Golding, Beveridge, & Glover, 2002; O'Connor, Heron, Golding, & Glover, 2003) from the Avon Longitudinal Study of Parents and Children (ALSPAC), which is a prospective, population-based study, with two assessments during pregnancy, found that anxiety in late pregnancy predicted hyperactivity and inattention symptoms in 4-year-old boys and at follow-up in 8-year-old boys and girls. Although these studies were well designed, interpretations of the results are clouded due to selective attrition (based on anxiety) as well as overall attrition due to missing data (43%), which can lead to over- or underestimation of effects.

Gender differences have been recently highlighted in research primarily because boys are over-represented in clinical samples, which may be due to a more difficult clinical presentation in boys (Biederman, Faraone, & Monuteaux, 2002), and less impairment is seen in girls (Newcorn et al., 2001). It may be possible that both males and females are affected, but in different ways (Coe et al., 2002).

The purpose of the present study was to prospectively investigate whether reports of smoking and stress during pregnancy predict symptoms related to ADHD in 7-year-olds while addressing specific past methodological limitations. One, because smokers tend to smoke more under stress (Epstein & Perkins, 1988) and perceived stress increases the likelihood of continued smoking during pregnancy (Rodriguez, Bohlin, & Lindmark, 2000), it is necessary to study smoking and stress together. Mattson and colleagues (Mattson, Calarco, Chambers, & KL, 2002) showed that merely controlling for one factor as a confounder does not fully reveal the effects of teratogens. We follow their recommendation and analyze independent effects of smoking and stress. Two, we assessed the 18 symptoms listed in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) for ADHD, rather than using a more general measure of child behavior problems. Three, we averaged data from two informants (mothers and teachers) in order to obtain a more complete picture of symptom presentation across environments. Four, repeated assessments of smoking and stress were made on 6 occasions (gestational weeks 10, 12, 20, 28, 32, and 36) throughout pregnancy. An advantage of having repeated measures is that we avoid problems associated with a single assessment and therefore we obtain a more accurate estimate of average smoking and stress exposure during pregnancy. Repeated measures gives us the possibility of studying effects of timing, an often recommended (e.g., Weinstock, 2001) but seldom tested strategy. Five, participants were recruited on a consecutive basis and were representative of the population. In sum, we sought evidence to link prenatal stress and/or smoking to ADHD symptoms while addressing some past limitations.

We expected that mean levels of smoking and or stress across pregnancy would be associated with ADHD symptoms measured as a continuous variable and as fulfillment of ADHD diagnostic criteria (categorical variable). Because prevalence is greater...
for boys, we expected that the strength of the association between prenatal exposure and ADHD-related problems would be stronger for boys than for girls. We also investigated the relative impact of the timing of exposure in predicting symptoms of ADHD.

**Methods**

**Participants**

Midwives from five prenatal health care clinics in Uppsala County, Sweden, solicited the participants at their first prenatal health care visit during December 1992 through March 1994. The clinics were chosen to be representative of the population in the county. Prenatal health care in Sweden is governmentally run at the primary health care level and is free of charge. Almost 100% of pregnant women receive such care (Åberg & Lindmark, 1992), thus there are no socio-economic differences among attendees. Women were consecutively recruited on the inclusion criteria that they were nulliparous and of Scandinavian origin; 91% agreed to participate. On average, the women were 27 years of age ($SD = 4$), had 4 years of secondary education, and had an annual income that corresponds to the Swedish national average for women of the same age (The National Board of Health and Welfare, 1996:2). The majority (91%) cohabitated with the expectant father. Birth outcomes in this sample (Rodriguez, Bohlin, & Lindmark, 2001) were similar to national norms (The National Board of Health and Welfare, 2002-125-12).

Of the 414 participants who delivered a live baby we were able to trace 393 at follow-up. We invited all women to participate who had live births and for whom current addresses were available. Ten declined (2.5%), 290 participated in the follow-up (74%), and the remainder did not respond. We obtained consent to contact the child’s teacher from 217 of the participating mothers (79%) and, of these, 208 teachers participated (96%). Thus, we obtained full data for 72% of the sample. Data were obtained for 142 boys (49.3%) and 146 girls. The gender of 2 children is unknown because one mother answered anonymously and the medical chart of the other mother was not registered in the country.

DSM scores for these children did not differ from the sample mean. At the time of follow-up, children had a mean age of 7 years and 8 months (i.e., 92 months; $SD = 4.66$). Teachers completed assessments approximately 2 months after mothers, when children had a mean age of 94 months ($SD = 4.39$).

Attrition analyses showed that follow-up participants did not differ from non-participants on data collected during pregnancy: stress ($t_{468} = .08$, ns), smoking ($t_{468} = 1.46$, ns), education ($t_{390} = .47$, ns), income ($t_{367} = 1.55$, ns), or civil status ($t_{3} = 1.40$, ns). The child’s gender was also unrelated to participation ($t_{2} = .46$, ns). Follow-up participants had slightly longer gestation (1.2 weeks: $t_{12} = 3.38$, $p < .01$), and consequently heavier infant birth weights ($t_{11} = 2.93$, $p < .01$). Neither gestational age nor birth weight was related to the outcomes; correlation coefficients ranged between 0 and .10. Those who granted us permission to contact the teacher did not differ from those who did not regarding the predictors, prenatal smoking ($t_{288} = -.86$, ns) and stress ($t_{286} = .10$, ns), or outcomes, DSM-IV scores as reported by mothers ($t_{287} = .59$, ns).

**Procedure**

Self-reports of prenatal exposures were collected in conjunction with regularly scheduled prenatal health care appointments during gestational weeks 10 ($M = 10.34$, $SD = 1.70$), 12 ($M = 12.71$, $SD = 1.57$), 20 ($M = 20.36$, $SD = 1.71$), 28 ($M = 28.00$, $SD = 1.16$), 32 ($M = 32.33$, $SD = .95$), and 36 ($M = 36.17$, $SD = .82$). Birth outcomes were abstracted from medical records. Approximately 7 years after delivery, we obtained women’s current addresses through the national registry and mailed a letter of invitation for the present study. Mothers provided written consent to contact the child’s teacher and supplied us with the teacher’s name and school address.

**Measures**

**Perceived stress.** The Swedish 10-item version of the Perceived Stress Scale (back-translated) (PSS; Cohen & Williamson, 1988) was used to measure global perceived stress, i.e., the degree to which situations in general are perceived as threatening, unpredictable, or uncontrollable. Items are rated on a 5-point scale ranging from never to experienced very often, during the previous 4-week period. The PSS is considered to be the only validated instrument that assesses appraisals of stress (Monroe & Kelley, 1995).

**Smoking.** Participants indicated on an 8-point scale the number of cigarettes they usually smoked on a daily basis within the last month at weeks 12, 20, 28, 32, and 36. Number of cigarettes was coded 0 (0 cigarettes), 1 (1–2 cigarettes), 2 (3–4 cigarettes), 3 (5–10 cigarettes), 4 (11–15 cigarettes), 5 (16–20 cigarettes), 6 (21–30 cigarettes), and 7 (more than 30 cigarettes). At week 10, women reported the number of cigarettes they smoked prior to knowing that they were pregnant.

**Demographics.** Information on various demographic variables was obtained via self-report (income and education) or via the medical chart (infant sex, maternal civil status and age).

**ADHD symptoms.** We used the 18 symptoms given in DSM-IV criteria for ADHD (APA, 1994), which is used in research (DuPaul et al., 1998). Each item was rated on a 3-point scale, 0 = never, 1 = sometimes, and 2 = often. We dichotomized each rating into present (1 or 2) vs. absent (0). We averaged the number of symptoms reported by mothers and teachers to form the continuous measure of ADHD symptoms. Thus, we obtained a measure that reflected variations in functioning across the two main environments to which children are exposed.

We administered the impact item of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1999) which consisted of a general question concerning difficulties with emotion, concentration, or behavior (item 26), and which if answered affirmatively is followed up by a question pertaining to duration (item 27) of
problems. The difficulties item discriminates very well between children with psychiatric disorders versus those without (Goodman, 1999). We dichotomized the duration item into 6 months or longer vs. shorter duration.

Fulfillment of the ADHD combined type criteria consisted of those listed in the DSM-IV: (1) the number of symptoms reached the required cutoffs (at least 6 out of 9 symptoms for each subtype), (2) symptoms reached the cutoffs in two environments, i.e., according to mothers and teachers, and (3) duration of problems lasted at least 6 months in both environments. Fulfillment of the criteria was scored one if all criteria were met, zero if none were met, and as missing if only some, but not all, criteria were met.

Statistical analyses

We averaged smoking and stress scores across pregnancy in order to obtain a measure that reflected the mean level of smoking during pregnancy and the mean level of perceptions of stress, regardless of the length of gestation. Correlational and multiple regression analyses were used to calculate the association between the predictors and ADHD symptoms on a continuous scale and tested whether sociodemographic variables had a confounding effect. Logistic regression analysis was used to test whether exposure to prenatal smoke or stress predicted fulfillment of ADHD diagnostic criteria. In order to test for possible timing effects, we entered assessments of stress and smoking in chronological order using hierarchical multiple regression analyses. The analyses determine whether each successive assessment made an independent contribution to the outcome.

Results

Descriptive data

The combined mean number of symptoms given by mothers and teachers (range 0 to 18) was 4.81 (SD = 4.30, n = 289). Mother and teacher reports were significantly correlated, \( r = .59, p < .0001 \). Combined mother and teacher reports showed that 17.8% of the sample was rated as having socio-emotional difficulties (SDQ item 26) and that for 16.0% these difficulties had lasted 6 months or longer (SDQ item 27 dichotomized).

Association to possible confounders

The child’s age at follow-up was unrelated to DSM score, \( r = -.04, \) ns. Maternal education \( (r = .14, p < .05) \) was the only demographic variable associated with ADHD symptoms. Maternal civil status during pregnancy \( (r = .04, \) ns), presence of a father figure in the home during follow-up \( (r = .01, \) ns), income during pregnancy \( (r = -.08, \) ns) and at follow-up \( (r = .04, \) ns) were unrelated to ADHD symptoms.

Of the women who participated at follow-up, 28% smoked prior to knowing they were pregnant and 14.5% continued to smoke during mid-pregnancy. Stress was normally distributed with a mean of 2.39 (SD = .53) on 1–5 scale, where 5 indicates high stress. There was a weak association between smoking and stress \( (r = .11, p < .06) \). Women who smoked during pregnancy had a greater likelihood of being single mothers \( (r = .20, p < .001) \), having lower salaries \( (r = -.17, p < .001) \) and lower education \( (r = -.22, p < .001) \). Perceived stress during pregnancy was associated only with income \( (r = -.18, p < .001) \).

Smoking and stress in relation to ADHD symptoms measured on a continuous scale

Table 1 presents the associations between maternal stress and smoking during pregnancy and ADHD symptoms in 7-year-olds. Symptom scores were associated with stress and smoking in the whole sample. However, these associations were mainly driven by boys because the link was not significant among girls. Partial correlation analyses controlling for demographics showed that all coefficients between ADHD symptoms and smoking and stress remained significant as before.

Multiple regression analyses revealed that both smoking and stress independently contributed to the variance in ADHD symptoms for the whole sample; stress \( (\beta = .17, p < .01) \) and smoking \( (\beta = .16, p < .01) \). The same was true in the separate analyses of boys; stress and smoking contributed independently \( (\beta = .24, p < .01 \) and \( \beta = .18, p < .02 \) and together they explained nearly 9% of the variance \( (adj \ R^2 = .0872) \) in ADHD symptoms. We re-ran regression analyses including each of the demographic variables (prenatal: maternal education, civil status, and salary, plus postnatal variables: salary and presence of father figure). None of these variables contributed independently to ADHD symptoms for the sample as a whole.

Smoking and stress in fulfillment of ADHD diagnostic criteria

We examined whether smoking and/or stress during pregnancy contributed to ADHD diagnostic criteria using logistic regression analysis. Seven children (all boys), i.e., 3.37% of the sample having complete

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pearson correlations between prenatal exposure to maternal stress and smoking and ADHD symptoms on DSM-IV inventory¹</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>DSM-IV Symptom score</td>
</tr>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Stress</td>
<td>.19**</td>
</tr>
<tr>
<td>Smoking</td>
<td>.18***</td>
</tr>
</tbody>
</table>

¹p<.05;  **p<.01; ***p<.001.
²Mother and teacher reports were averaged.
data, fulfilled all of the criteria for the ADHD combined type and 121 children fulfilled none of the criteria.

Table 2 presents results of logistic regression analyses. We first conducted univariate analyses entering either smoking or stress. The results at the top of the table show that the contribution of smoking when entered alone was nearly significant and that stress was clearly significant. We calculated effect size (Clark-Carter, 1997) and found a large effect for stress (Cohen’s $d = 1.20$) and a moderate effect for smoking (Cohen’s $d = .71$). The bottom half of the table presents the multivariate equation entering both smoking and stress and shows that only stress contributed independently to ADHD diagnostic criteria, that nearly 87% of the cases were concordant and that somewhat more than 23% of the variance was explained.

### Effect of timing of stress and smoking

To test for temporal effects in ADHD symptoms (continuous measure), we conducted hierarchical multiple regression analyses for the whole sample, entering each predictor in chronological order. Multicollinearity may be a problem when entering chronological scores that are highly correlated. Correlation coefficients ranged between $r = .54$ (gestational weeks 10 and 36) and $r = .81$ (gestational weeks 32 and 36) for stress and between .55 and .92 for smoking. Because intercorrelations were too high for smoking (Cohen & Cohen, 1983), we pooled the data to represent smoking in the first half vs. the second half of pregnancy ($r = .78$, $p < .0001$). Smoking during the first half of pregnancy was significant ($\beta = .16$), but smoking during the latter half did not explain further variance. Similarly, stress at the beginning of pregnancy (gestational week 10) accounted for the largest portion of variance ($\beta = .20$), and additional assessments did not explain further variance.

### Discussion

By studying both prenatal smoking and stress as independent factors, we were able to observe whether these two pathways contributed to ADHD symptoms in 7-year-olds. We examined symptoms on a continuous scale, according to combined mother and teacher reports, and found that prenatal exposure to stress and smoking were independently associated with ADHD symptoms listed on the DSM-IV for the whole sample and particularly among boys. Associations did not reach significance for girls. The link between prenatal exposure to smoking and stress and ADHD symptoms was not confounded by sociodemographic factors. When we examined whether prenatal exposure to smoking and stress was related to fulfillment of the diagnostic criteria for ADHD, we found a link between prenatal stress exposure, independent of smoking. Nearly 87% of the cases were correctly predicted (concordant). Only boys fulfilled all the necessary criteria for ADHD in our sample.

Taken together, the results concerning stress are compelling because stress was related to both ADHD symptoms on a continuum and ADHD diagnostic criteria. The effect size of stress on fulfillment of diagnostic criteria was large. Results are less clear for smoking. We found a significant association between smoking and ADHD symptoms which was independent of stress. Smoking had a modest effect size on ADHD criteria, but no significant independent association after including stress in the logistic multiple regression analyses. It seems likely that we lacked statistical power. Prevalence of smoking was low in this sample (Rodriguez et al., 2000), consistent with national norms (The National Board of Health and Welfare, 2000-77-050). The number of women experiencing stress is likely to be higher than the portion of women smoking in the population, and so stress becomes a more probable teratogen with relevance for public health.

We found that slightly more than 3% of the sample fulfilled the criteria for ADHD. Because these children were boys, the prevalence for boys was 6.7%. We found support, as hypothesized, for the prediction that the association between prenatal exposure and ADHD would be stronger for boys than for girls. The clear gender differences in our findings may be due to male fetuses’ heightened vulnerability to adversity (Jakobovits, 1991) or to females’ hardiness. Researchers postulate that gender differences in behavioral manifestations correspond to neurophysiological differences seen in human and animal studies in which males show an overproduction and

### Table 2 Results of univariate and multivariate logistic regression analyses entering smoking and stress as predictors of fulfillment of ADHD-combined type vs. non-fulfillment

<table>
<thead>
<tr>
<th>Effect size</th>
<th>$\beta$</th>
<th>$p$-value</th>
<th>$R^2$ model</th>
<th>Max rescaled $R^2$</th>
<th>OR</th>
<th>95% CI</th>
<th>% concordant</th>
<th>% discordant</th>
</tr>
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<tbody>
<tr>
<td><strong>Univariate analyses</strong></td>
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<tr>
<td>Smoking</td>
<td>.71</td>
<td>.24</td>
<td>.07</td>
<td>.06</td>
<td>.06</td>
<td>1.08</td>
<td>.99–1.17</td>
<td>39.6</td>
</tr>
<tr>
<td>Stress</td>
<td>1.20</td>
<td>.74</td>
<td>.004</td>
<td>.22</td>
<td>.22</td>
<td>11.64</td>
<td>2.14–63.23</td>
<td>86.1</td>
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<tr>
<td><strong>Multivariate analyses</strong></td>
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<tr>
<td>Smoking</td>
<td>14</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td>1.04</td>
<td>.95–1.15</td>
<td>86.9</td>
</tr>
<tr>
<td>Stress</td>
<td>.68</td>
<td>.01</td>
<td>.0814</td>
<td></td>
<td>.2343</td>
<td>9.30</td>
<td>1.65–52.38</td>
<td></td>
</tr>
</tbody>
</table>

Note: Effect size (Clark-Carter, 1997) and found a large effect for stress (Cohen’s $d = 1.20$) and a moderate effect for smoking (Cohen’s $d = .71$).
subsequent pruning of dopamine receptor density (striatal D1 and D2 receptors) in comparison to females and that overproduction corresponds to hyperactive behavior (Andersen & Teicher, 2000). Another possibility is that both males and females are affected, but in different ways, as was concluded in a study of prenatal stress (Coe et al., 2002). Our study was not designed to test for outcomes other than ADHD but future studies should address this issue.

We also sought to investigate whether the timing of smoke or stress exposure during pregnancy had an impact on ADHD symptoms as measured on a continuous scale. We tested assessments in chronological order while controlling for preceding assessments. We found that for both stress and smoking significant associations were found only for exposures in the beginning or first half of pregnancy, respectively, and that later exposure did not account for further independent variance. There are several explanations for our findings. First, it is difficult to adequately test timing, e.g., smoking is unlikely to be initiated or substantially increased in the latter half of pregnancy (given public awareness) in comparison to the first half. Second, the amount of smoking or stress exposure in early pregnancy may be a marker for chronicity. Intercorrelations among the assessments over time were high. Yet another explanation for our results may be that exposure in early pregnancy is more adverse than later exposure. This conclusion is supported by studies of natural disasters, e.g., famine (Roseboom et al., 2000) and stress related to earthquake (Glynn, Wadhwa, Dunkel-Schetter, Chicz-DeMet, & Sandman, 2001), which found that exposure to adversity during early gestation was more strongly associated with negative outcome than later exposure. In this case, our results are important because exposures at the beginning of pregnancy may set the stage for later development and so are relevant for health recommendations to pregnant women.

We attempted to resolve past methodological limitations and succeeded on several counts; however, shortcomings are still present and our results should be viewed in light of these. The major limitation is that although we were able to follow up a relatively large number of children, our sample size restricted our statistical power. This is particularly important when overall prevalence in the population is low as in ADHD (below 10%), and even lower among girls, and so our ability to detect significant effects is limited. The sample was nonetheless representative because sample characteristics were comparable to national statistics and attrition was not selective on key variables. Careful assessment of prenatal exposures is an important consideration in relation to statistical power. Because we used a repeated measures design, our results are unlikely to be a consequence of random variation in smoking or stress exposure at any given point during pregnancy, but rather represent the average exposure across pregnancy. Moreover, stress exposure was measured using a validated instrument.

Another limitation was that we were unable to investigate familial history of ADHD. We attempted to do so by asking mothers if they or the child’s father had been diagnosed with a childhood psychiatric disorder. The obtained frequencies were so low that statistical analyses were precluded. None of the children who met the diagnostic criteria had a positive familial history; nonetheless, we are unable to rule out possible genetic transmission. Familial history of ADHD is important because ADHD has been linked to smoking in adulthood (Pomerleau et al., 2003) and so genetic composition may account for both smoking in the parent and ADHD symptoms in the child. A more fruitful approach in the future would be to assess ADHD in parents using a validated instrument for adults or to include prenatal exposures as independent factors in genetic studies of ADHD.

The lack of inclusion of postnatal measures can be viewed as a shortcoming. Certain child behavior problems have been associated with social adversity (Biederman et al., 2002) and postnatal smoking (Maughan, Taylor, Taylor, Butler, & Bynner, 2001). The postnatal environment is likely to play a modifying role, either ameliorating or aggravating the development of difficulties for individuals with an underlying predisposition. Our focus in the present study was on teratogens during brain formation. Because ADHD is believed to be a biologically based disorder (Spencer, Biederman, Wilens, & Faraone, 2002), such teratogens are of utmost importance. As outlined by Slotkin (1998), receptor stimulation during brain development is uniquely different than stimulation to a non-developing system inasmuch as gene expression is altered in the former case. Perturbations during prenatal brain development may lead to far-reaching disturbances in CNS function that are not detectable at birth (Thomas, Garrison, Slawecki, Ehlersand, & Riley, 2000). Our findings are consistent with Slotkin’s conclusions because smoking was related to ADHD symptoms even though birthweight was unrelated to symptoms. Moreover, our findings extend Slotkin’s theory to include stress. Approximately 40% of maternal cortisol crosses the placenta (Gitau, Cameron, Fisk, & Glover, 1998) and may thus affect the developing fetal brain as has been found in experimental animal studies.

In sum, our results point to independent contributions of stress and smoking on symptoms of ADHD and of stress on fulfillment of ADHD diagnostic criteria among boys. The magnitude of the associations between prenatal exposure and behavior problems was greater for boys than for girls. The fact that we studied a representative sample using a prospective and rigorous methodology, including repeated assessments of exposures throughout
pregnancy, increases the significance of our findings and highlights the importance of the prenatal environment. Because many women smoke or experience stress during pregnancy and because this is, to a certain extent, preventable, our results are of public health concern.

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Correspondence to
Alina Rodriguez, Uppsala University, Department of Psychology, Box 1225, SE-751 42 Uppsala, Sweden; Tel: +46 18 471 7980; Fax: +46 18 471 2123; Email: Alina.Rodriguez@psyk.uu.se

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